Attorney Docket No. 056100-5027-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

LEE

Serial No.: 08/971,338

Filed: November 17, 1997

Title: GDF-1 PROTEIN

Group Art Unit: 1680

Examiner: M.P. Allen

#28
Plunkett
3/26/03
1643

DATE: March 21, 2003

APPELLANT'S APPEAL BRIEF

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Introduction

The invention on appeal encompasses isolated mammalian GDF-1 proteins and processes for purifying the same.

Real Party in Interest

The real party in interest is the Carnegie Institution of Washington by virtue of assignment from the inventor, Dr. Se-Jin Lee, recorded at Reel 5582, Frame 0797 on January 16, 1991. An exclusive license is currently held by Curis, Inc.

Related Appeals and Interferences

There are no related interferences known to the appellant, his legal representatives or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal. An appeal is being concurrently filed in related divisional application Serial No. 08/966,233.

Status of Claims

Claims 1-21 were presented with the application as filed and claims 22-35 were added by amendment. Of these claims, claims 1-3, 11-21 and 34-35 have been canceled. It should be noted that an amendment after final was submitted concurrently with this brief, canceling claims 34 and 35 and incorporating the limitations recited therein into claims 4 and 24, respectively. This amendment narrows the issues for appeal and entry of the amendment is expected. This Appeal Brief assumes entry of the concurrently filed amendments. Thus claims 4-10 and 22-33 are presented as amended and being pending and at issue in this appeal. These claims are set out in an Appendix to this brief (Exhibit A).

Status of Amendments

The appellant submitted a response dated July 12, 2002 with arguments in response to the non-final Office Action dated March 12, 2002. This response was entered and considered in the Final Office Action dated October 21, 2002. The appellant filed a Notice of Appeal on January 21, 2003. An amendment after final is submitted concurrently with this brief. Entry of the amendment is expected as it narrows the issues for appeal.

Summary of the Invention

In concise form, the invention of the pending claims is directed to the isolation of mammalian GDF-1 proteins, and methods of purifying the same.

The GDF-1 gene was isolated by virtue of its homology to the transforming growth factor beta (TGF-β) superfamily. A growing number of polypeptide factors playing critical roles in regulating differentiation processes during embryogenesis have been found to be structurally homologous to the TGF-β superfamily (see the Background of the Invention in the specification). Potential uses for GDF-1 as a therapeutic and diagnostic tool are suggested based on the known biological activities of other members of this superfamily (pages 12-14 of the specification and particularly page 13, lines 16-18).

The sequence for murine GDF-1 was originally isolated from a cDNA library prepared from day 8.5 embryos, which was screened using oligonucleotides selected on the basis of amino acid sequences of conserved regions among members of the TGF-β superfamily (see Example 1 of the specification, page 18). The sequence of one 1.4 kb GDF-1 clone obtained is shown in Figure 2, and contains a single long open reading frame encoding a protein of 357 amino acids with a predicted molecular weight of 38,600 daltons, beginning with an initiating ATG codon at nucleotide 217. Two other clones from the library were sequenced, and are believed to represent allelic variations within the gene (see page 19, lines 17-29).

A comparison of the C-terminal region of the GDF-1 protein with other members of the TGF-β superfamily is shown in Figure 3a. The GDF-1 sequence contains all of the invariant amino acids present in the other members, including the seven cysteine residues with their characteristic spacing, and a pair of arginine residues at positions 236-237. The level of homology observed between GDF-1 and the other members of the TGF-β superfamily (26-52%) was high enough to assign GDF-1 to this family but not so high so as to suggest that GDF-1 was a homologue of a previously-identified TGF-β family member (see page 20, lines 7-30).

Translation of the full length GDF-1 RNA *in vitro* resulted in a protein species of 39.5 KDa, which agreed well with the predicted molecular weight of 38.6 Kda (see page 21, lines 9-16. When full length GDF-1 RNA was translated in the presence of dog pancreas microsomes, a slower migrating 41KDa form was detected. The 41 KDa form could be converted to a 38 KDa species upon treatment with endoglycosidase H, suggesting that the 41 KDa and 38 KDa forms represented glycosylated and unglycosylated forms.

To determine whether GDF-1 is encoded by a single copy gene, Southern hybridization to mouse genomic DNA was carried out using the GDF-1 cDNA as a probe (see Example 3, page 22). A predominant band was identified in three different digests of mouse genomic DNA. Further, the GDF-1 probe also detected a single prominent band in both human and hamster genomic DNA, even at high stringency, suggesting that GDF-1 is highly conserved across species (page 22, lines 24-32).

When the inventors examined GDF-1 expression in embryos, a 1.4 kb transcript was observed in embryos at day 8.5 and 9.5, but not in later stage embryos. A second mRNA species, 3.0 kb in length, appeared at day 9.5 and persisted throughout embryogenesis (page 23, lines 9-13). Examination of adult animals showed that the 3.0 kb transcript was also present almost exclusively in the central nervous system of adult animals (pages 23-24). The 3.0 kb transcript was cloned from a murine adult mouse brain cDNA library, and was shown to contain both the 1.4 kb segment comprising the GDF-1 open reading frame, and a 1527 base pair region upstream (Example 7, page 28). This upstream region was found to contain a second long open reading frame beginning with an initiating ATG codon at position 74, extending 350 codons, and terminating 404 base pairs upstrem of the GDF-1 open reading frame. This second open reading frame was designated UOG-1 (upstream of GDF-1) (see paragraph bridging pages 29-30). A search of the NBRF and GenBank sequence databases revealed no known sequences with significant homology to UOG-1 (page 30, lines 5-10). Figure 11A shows the complete sequence of a mouse 2.7 kb clone containing both the UOG-1 and GDF-1 open reading frames.

Human GDF-1 cDNAs were also isolated from adult cerebellum and fetal brain cDNA libraries using the murine GDF-1 cDNA as a probe (Example 8, page 30). Figure 11B shows the sequence of a 2510 base pair human cDNA containing the open reading frame for human GDF-1 beginning at nucleotide 1347 and an upstream open reading frame that is 81% identical on the amino acid level to murine UOG-1. The murine and human sequences are 87% identical in the region beginning with the first conserved cysteine and extending through the C-terminus, and 69% identical through the entire length of the proteins. Southern hybridization to genomic DNA was performed to verify that the human GDF-1 gene is indeed the homolog of the mouse GDF-1 gene (see paragraph bridging pages 31-32).

Example 6, beginning on page 25 of the specification, provides a protocol for cloning GDF-1 into an expression vector and expressing GDF-1 in a host cell to produce recombinant GDF-1 protein. A procedure for purifying the GDF-1 protein using standard purification techniques is provided on page 27, lines 15-37.

Thus, the pending claims are fully supported by the appellant's original disclosure.

The Issues

(1) Utility and Enablement

The Examiner has finally rejected claims 4-10 and 22-35 under 35 U.S.C. §101 because the invention is allegedly not supported by a specific, substantial and credible utility or by a well established utility. The Examiner has made a corresponding rejection of these claims under 35 U.S.C. §112, first paragraph for lack of enablement, alleging that since the claimed invention is not supported by a utility, one of skill in the art would not know how to use the claimed invention. Since the Examiner has supported these rejections with a single argument, the rejections are considered in this brief as a single issue. On this basis, the issue can be stated as follows:

> Are the appellant's claimed proteins lacking in either a specific, substantial and credible utility or a well-established utility such that one of skill in the art would not know how to use the claimed invention?

The appellant submits that the claimed proteins are supported by a specific, substantial and credible utility such that the skilled artisan would know how to use the claimed invention for reasons detailed herein.

(2) Written Description

The Examiner has finally rejected claims 4-7, 22, 24-25, 30 and 34-35 under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. The Examiner's general basis for the rejection is that appellant has not provided defining structural or functional features for GDF-1 and therefore the appellant has not described the invention as broadly as claimed. In particular, the Examiner asserts that disclosure of Southern hybridization and description of a domain would not convey to one of ordinary skill in the art that the invention contemplated was that which is presently claimed. The issue can be stated as follows:

Has the appellant provided defining structural or functional features of a GDF-1 protein so as to provide adequate description for the claimed genus directed to mammalian GDF-1 proteins?

For the reasons detailed below, the appellant submits that the specification provides defining structural features of a GDF-1 protein so as to provide support for the claimed genera, and furthermore, that the skilled artisan would recognize that the appellant was in possession of the claimed genera at the time the application was filed.

(3) New Matter

The Examiner has finally rejected claims 34-35 under 35 U.S.C. §112, first paragraph, for allegedly containing new matter. Specifically, the Examiner asserts that the appellant has not pointed to a page and line number showing support for these claims. On this basis, the issue can be stated as follows:

Do claims 34-35 (now incorporated into amended claims 4 and 24) contain new matter so as to be unpatentable under 35 U.S.C. §112, first paragraph, for lack of written description?

For the reasons detailed below, the appellant submits that claims 4 and 24 do not contain new matter, and that appellant has provided page and line number support for these claims.

Grouping of Claims

Claims 4-10 and 22-33 may be considered together with regard to the utility and enablement (how to use) arguments.

Claims 4-7, 22, 24-25, 30 and 33 may be considered together with regard to the written description arguments.

Claims 4 and 24 may be considered together with regard to the new matter rejection.

Arguments

(1) Utility and Enablement

The Examiner has finally rejected claims 4-10 and 22-35 under 35 U.S.C. §101 because the invention is allegedly not supported by a specific, substantial and credible utility or by a well established utility. The Examiner has made a corresponding rejection of these claims under 35 U.S.C. §112, first paragraph for lack of enablement, alleging that since the claimed invention is not supported by a utility, one of skill in the art would not know how to use the claimed invention. The appellant respectfully requests that the Board reverse this rejection.

As described in the Background Information section at page 1, lines 15-19, a growing number of polypeptide factors playing critical roles in regulating differentiation processes during embryogenesis have been found to be structurally homologous to transforming growth factor β (TGF-β). Further, as reiterated at page 2, lines 23-28 of the specification, the invention relates to a new member of the TGF-β superfamily, which, like other members of this superfamily, is predicted to play an important role in mediating developmental decisions related to cell differentiation.

As further described on page 12 of the specification, beginning at line 10:

> The structural homology between GDF-1 and the known members of the TGF-β superfamily and the pattern of expression of GDF-1 during embryogenesis indicate that GDF-1 is a new member of this family of growth and differentiation factors. Based on the known properties of the other members of this superfamily, GDF-1 can be expected to possess biological properties of diagnostic and/or therapeutic benefit in a clinical setting.

The specification goes on to provide several potential uses for GDF-1 based on the observed homology to the TGF-β superfamily, including diagnostic use as an indicator for the presence of developmental anomalies in prenatal screens for potential birth defects (page 12, lines 32-35). This proposed use is directly related to the predicted role of GDF-1 in embryogenesis, and is supported by the fact that other members of the TGF-β superfamily known at the time had each been shown to play a pivotal role in embryonic processes. See Akhurst *et al.*, 1990, Prog. Growth Factor Res. 2(3): 153-68 (abstract) (attached as Exhibit B).

In the Office Action dated March 12, 2002, the Examiner dismissed the noted homology of GDF-1 proteins to the TGF-β superfamily as failing to provide the requisite utility, because

the activities of the TGF-β superfamily members "vary quite widely" and "some TGF superfamily members have diverse activities in embryonic development and some have no role in development" (Office Action, pages 4 and 5, respectively). The Examiner provided no documentary evidence to support this assertion.

Appellant respectfully notes that the Akhurst reference was published in 1990, which is the year that the earliest priority application to the present application was filed. Therefore, the Akhurst reference is an appropriate measure of what was known in the art relating to transforming growth factors at the time the application was filed. According to the Akhurst abstract, "each" of the TGF-β superfamily members identified at that time plays "a pivotal role" in embryonic processes. There is no suggestion that other TGF-β family members known at that time played a role that did not relate to development, and the Examiner has provided no evidence to suggest that TGF-β members known at that time were thought to "have no role in development."

Thus, at the time the present application was filed, the TGF-β superfamily had been characterized as "a large superfamily of related proteins, each of which plays a pivotal role in embryonic processes" (Akhurst). It is Appellants' understanding upon a reading of the utility guidelines (FR, Vol. 66, No. 4, January 5, 2001) (Exhibit C) that it is perfectly acceptable to assert a specific, substantial and credible utility on the basis of "homology to existing nucleic acids or proteins having an accepted utility." According to the FR Notice, a rigorous correlation is not necessary; only a "reasonable" correlation (see the FR Notice, page 1096, middle column continuing into right-hand column). As stated therein, "When a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein" (with emphasis). Id.

The Examiner has not disputed the reasonable assignment of GDF-1 to the TGF-β superfamily. As acknowledged by the Examiner, GDF-1 proteins are 26-52% similar to TGF-β family members on the amino acid level (Office Action dated March 12, 2002, page 4). Moreover, according to the specification at the paragraph bridging pages 19-20, GDF-1 contains all of the invariant amino acids present in the C-terminal 122 amino acids of other TGF-β

superfamily members, including the seven characteristic cysteine residues as well as many of the other most highly conserved amino acids. For instance, like the other family members, the C-terminal portion of the predicted GDF-1 polypeptide is preceded by a pair of arginine residues at positions 236-37. Thus, GDF-1 contains sufficient homology to be reasonably assigned to the TGF-β superfamily.

According to the new utility guidelines, "the asserted utility must be accepted by the examiner unless the Office has sufficient or sound reasoning to rebut such an assertion." Id. (with emphasis). The Examiner rejects the asserted utility on the basis that the members of the TGF-β family exhibit diverse activities, and that some members have roles not related to embryonic development. However, the Examiner provides no evidence that those of skill in the art at the time the invention was made would have believed that members of the TGF-β super family exhibit such diverse activities as to preclude prediction of function based on this family assignment. In contrast, according to the Akhurst abstract, there had been five type beta transforming growth factors (TGF-βs) identified at the priority date of the invention, each of which was found to play "a pivotal role in embryonic processes."

Thus, at the time the invention was made in 1990, one of skill in the art would have reasonably predicted that a member assigned to the TGF-β superfamily would play a role in embryonic development, and in the growth and differentiation of tissues, given that at least five TGF-β members identified at that time were shown to play a "pivotal role" in embryonic development. Indeed, as mentioned above, according to the instant specification at page 1, "a growing number of polypeptide factors playing critical roles in regulating differentiation processes during embryogenesis [had] been found to be structurally homologous to transforming growth factor B." On that basis, and in view of the homology of GDF-1 to TGF-β, the appellant predicted that the GDF-1 protein was likely to play an important role in mediating developmental decisions related to cell differentiation (see page 2, lines 25-29). Moreover, it was perfectly reasonable on the basis of that prediction and the homology demonstrated according to the rules promulgated by the Office for Applicants to assert that the claimed protein would find utility in prenatal screens to detect developmental abnormalities, as disclosed on pages 12-13 of the specification.

The reasonable assignment of utilities based on predicted role in embryonic development is further confirmed by recent experiments that show that, in fact, the appellant's predictions were correct. As the present inventor and others have shown in a recently published paper (Rankin *et al.*, 2000, Regulation of left-right growth patterning in mice of growth/differentiation factor-1, Nature Genetics 24: 262-66) (Exhibit D), GDF-1 plays a pivotal role in embryogenesis. A knockout mouse was generated in order to examine the biological function of GDF-1, which exhibited a spectrum of defects related to left-right axis formation in embryos, including misplacement of internal organs (Fig. 2), developmental defects in organs and cardiac abnormalities (Fig. 3). The authors concluded that these findings indicate that GDF-1 is essential for proper establishment of the left-right axis in mice, and is required for the expression of many genes expressed downstream from GDF-1 during development.

The Examiner dismisses the Rankin reference because it was published well after the filing date of the invention, and because knock-out mice were not routinely produced at the time of the invention (Office Action, March 12, 2002, page 5). It is appellant's understanding, however, that it is acceptable to submit evidence gathered after the filing date to prove the adequacy and accuracy of the specification disclosure. The Rankin reference was submitted to demonstrate that the GDF-1 protein has the utilities that were predicted in the specification, and is suitable evidence for that purpose even though it was published after the filing date of the present application.

Thus, results with the GDF-1 knockout mouse prove that GDF- 1 is required for the proper development and positioning of organs during embryogenesis. This is consistent with the function of GDF-1 predicted in the specification (page 2, lines 25-29), and the results in the specification showing the expression of GDF-1 during embryogenesis (see Example 4 and Fig. 6). These results also confirm that the asserted utility of GDF-1 in prenatal screens for abnormal development is a reasonable utility for the disclosed nucleic acid, given that it has now been confirmed that aberrant expression of GDF-1 has significant and substantial effects on embryonic development.

In the Office Action dated October 21, 2002, the Examiner argues that one of skill in the art would not interpret the gene expression results in Example 4 and Figure 6 as a prediction that

the biological role of GDF-1 would be the regulation of left-right patterning or axis formation in mice (page 3). However, the appellant has not asserted that the specification teaches that GDF-1 regulates left-right patterning or axis formation in mice. Rather, appellant predicted in the specification that GDF-1 plays a role in embryonic development, and the showing in Rankin *et al.* that GDF-1 specifically regulates left-right patterning and axis formation during embryonic development is proof that appellant's prediction was correct.

The Examiner further argues that the information in the specification does not suggest or predict a prenatal condition that GDF-1 could be used to screen for (Office Action dated October 21, 2002, page 3). This is not correct, however, because the specification discloses at the paragraph bridging pages 12-13 that abnormal levels of GDF-1 could be associated with developmental anomalies or structural defects in the developing fetus.

Thus, at the time the application was filed, the TGF-β superfamily was known to comprise proteins involved in embryonic development, a function that appellant predicted that GDF-1 would share. Further, appellant has demonstrated according to published evidence (Rankin *et al.*) that GDF-1 does possess the predicted function, thereby supporting the disclosed utilities, *i.e.*, use in prenatal screening for developmental defects. And as noted above, according to the utility examination guidelines, it is perfectly acceptable to predict a specific, substantial and credible utility on the basis of homology to an established family of nucleic acids or proteins having an accepted utility. The claimed proteins are therefore supported by the specific, substantial and credible utility as a marker for the presence of embryonic developmental and structural defects, and the skilled artisan would therefore know how to use the claimed invention.

The appellant has offered evidence of other utilities disclosed by the specification over the course of prosecution that have also been dismissed by the Examiner. For instance, as described in the specification at the top of page 14, "If GDF-1 possesses a similar activity [as the TGF-β family member, activin], as is indicated by its specific expression in the central nervous system, GDF-1 will likely prove useful *in vitro* for maintaining neuronal cultures." To demonstrate that GDF-1 possesses the predicted function, the appellant submitted a declaration pursuant to 37 CFR §1.132 by Dr. Ted Ebendal (Exhibit E) on April 24, 1998, describing

experiments showing that GDF-1 has a biological activity on neurons in culture similar to other TGF-β family members.

The Examiner indicated that the Ebendal declaration was not sufficient because the information presented in the declaration was not known at the time the application was filed (Office Action, October 3, 2000, page 7). Again, it is the appellant's understanding that it is perfectly acceptable to submit evidence gathered after the filing date of the application to demonstrate that the utilities predicted in the specification were correct. The Ebendal declaration is therefore suitable evidence supporting the predicted activity of GDF-1 as a cell survival molecule in the *in vitro* culturing of neurons and is acceptable evidence rebutting the rejection.

Further, as described in the Appeal Brief submitted July 3, 2000, GDF-1 proteins are also useful as cell lineage markers. Indeed, as stated in the specification at page 12, lines 20-23, "One potential use for GDF-1 as a diagnostic tool is as a specific marker for the presence of tumors arising from cell types that normally express GDF-1." Figure 7 of the specification shows that GDF-1 is expressed almost exclusively in the brain. Thus, detection of a GDF-1 protein in tumor tissue may be used to determine for instance whether a brain tumor is a primary tumor or a metastasis from a tissue that does not express GDF-1. Such a determination has diagnostic and therapeutic consequences for cancer treatment, and is fully enabled by the showing of the tissue expression profile of GDF-1 in the original specification.

In view of all the remarks above, the appellant submits that the claimed invention is supported by at least one specific, substantial and credible utility, therefore, the skilled artisan would know how to use the claimed invention.

(2) Written Description

The Examiner has finally rejected claims 4-7, 22, 24-25, 30 and 34-35 under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the invention. The Examiner's basis for the rejection is that the appellant has not provided defining structural or functional features for GDF-1 and therefore the appellant has not described the invention as broadly as claimed. In particular,

the Examiner asserts that disclosure of Southern hybridization and description of a domain would not convey to one of ordinary skill in the art that the invention contemplated was that which is presently claimed.

At the outset, it should be noted that claims 34 and 35 have been cancelled, and the limitations recited therein have been incorporated into claims 4 and 24, respectively. Thus, claim 4 is now directed to a mammalian GDF-1 protein substantially free of proteins with which it is naturally non-covalently associated, wherein said protein is encoded by a nucleic acid that hybridizes under conditions of 65°C and 1M sodium chloride to DNA having the nucleotide sequence as defined in Figure 2 or Figure 11A or 11B and remains bound when subjected to washing at 68°C and 0.3 M sodium chloride/ 30 mM sodium citrate (2X SSC).

In setting forth the rejection, the Examiner disputed that the invention "contemplated" was that which is presently claimed. The appellant believes that it is quite clear from the specification that the presently claimed genus comprising mammalian GDF-1 proteins was the invention contemplated in the specification. For instance, according to the Summary of the Invention, in one embodiment, the present invention relates to a DNA segment encoding all, or a unique portion, of "mammalian" GDF-1 (page 3, lines 1-3). Further, according to the Detailed Description section of the specification, the invention relates to GDF-1 proteins and allelic and "species variations" thereof (page 9, lines 18-20). Thus, it is clear from the specification that the inventor "contemplated" the genus of mammalian GDF-1 proteins that is presently claimed. The pertinent question is whether the specification conveys that the inventors were in possession of the claimed genus at the time the application was filed.

The Examiner asserts that no structural features were identified in the specification that could be used to define a GDF-1 protein, and that the application teaches no assays for functional identification (Office Action, June 19, 2001, page 5). Appellant respectfully notes that the specification discloses amino acid sequences for GDF-1 proteins from both human and mouse, and also provides the sequences of several allelic variants that were separately cloned (see Examples 1, 7 and 8 in the specification, and particularly page 19, lines 17-29, and the paragraph bridging pages 28-29). Further, the specification discloses that the human and murine GDF-1 proteins are 87% identical in the region beginning with the first conserved cysteine and

extending to the C-terminus (see page 31, lines 19-20). Thus, this specific domain of GDF-1 is quite highly conserved across species, and would constitute a structural feature for identifying a mammalian GDF-l gene.

Furthermore, the instant specification shows that a probe generated from the full length murine open reading frame of GDF-1 hybridizes specifically to the human gene in Southern hybridization (see Fig. 14 legend at page 9, and the relevant discussion at pages 31-32). As also shown in Figure 5, even at high stringency, a murine GDF-1 probe identified a single prominent band in both human and hamster genomic DNA. The genomic sequences identified by these hybridization experiments could be readily cloned and sequenced to obtain the corresponding protein sequence using techniques that were well known at the time the application was filed.

During prosecution, the Examiner cited a variety of case law for the unusual premise that the actual protein sequence itself must be disclosed for every sequence falling within the scope of the claims, including *University of California v. Eli Lilly,* 43 USPQ2d 1398 (see Office Action, October 3, 2000 (page 11)). The appellant respectfully submits that the merits of each case must be examined on a case-by-case basis, and *Lilly* does not suggest otherwise. Moreover, *Lilly* is only relevant to the particular circumstances surrounding that case, which happened to occur at a time when the art of biotechnology was much less developed than it is now. In fact, the present application was filed after the publication of the popular Sambrook Molecular Cloning manual (2nd edition), which standardized many of the cloning procedures now used to identify and isolate genomic DNAs and other related DNA species using a particular cDNA probe. Indeed, given the existence of the Sambrook manual at the time the present invention was filed, and the showing of species cross-hybridization using the probes described in the specification, those of skill in the art would have surely seen that the inventor was in possession of the claimed genus of GDF-1 proteins upon reading the present disclosure.

For instance, according to the pages from Sambrook *et al.*, 1989, Molecular Cloning: A Laboratory Manual (2d edition) (Exhibit F), libraries generated from mammalian genomic DNA had been in use since the mid-1970's for cloning mammalian genes (see page 9.2). And according to the teachings on page 9.3, it was well-known at the time this Manual was published that one could use libraries of randomly cleaved DNA to "walk" along the eukaryotic

chromosome starting with a single specific probe, in order to isolate segments of DNA in and around target sequences without knowledge of the location of surrounding restriction sites.

Further, according to Sambrook *et al.* on page 8.46, nucleic acid hybridization is "the most commonly used and reliable method of screening cDNA libraries for clones of interest . . . [A]s a result of more than twenty years of work, the theoretical basis of nucleic hybridization is well-understood." In particular, partially homologous probes were commonly used at the time Sambrook *et al.* was published to detect cDNA clones that are related, but not identical, to the probe sequences. For example, if the same gene has already been cloned from another species, Sambrook *et al.* suggests performing a series of Southern hybridizations at different stringencies to determine the conditions that will allow the previously cloned gene to be used as a probe for isolating the corresponding cDNA from another species (see page 8.47). The corresponding cDNA is then isolated from a cDNA library and validated using any of the methods described on page 8.51 of Sambrook *et al.* In particular, the open reading frame of the cDNA may be sequenced to determine the corresponding amino acid sequence.

Thus, it was common practice at the time the present application was filed to isolate related nucleic acids using hybridization techniques, and to sequence the related nucleic acids to obtain the encoded protein sequence. Further, it was common practice at the time the present application was filed to produce the encoded proteins from such isolated nucleic acids using recombinant technology, such as that described in the present specification (see Example 6). The Written Description Guidelines (FR, Vol. 66, No. 4, page 1099, January 5, 2001) (Exhibit G) specify that such common techniques need not be described, because one of skill in the art would be familiar with such techniques and would incorporate such knowledge into his understanding as to what the inventor possessed at the time of filing.

To illustrate, in the Federal Register publication of the Written Description Guidelines for Examination, the Office answered one comment by stating that "[a]ctual reduction to practice may be crucial in the relatively rare instances where the level of knowledge and level of skill are such that those of skill in the art cannot describe a composition structurally, or specify a process of making a composition by naming components and combining steps" (with emphasis, see page 1101). In fact, the Guidelines state at page 1106 that:

> An applicant may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. (With emphasis.)

Footnote 42 of the Guidelines further defines some identifying characteristics for biomolecules to include sequence, structure, binding affinity, binding specificity, molecular weight, length, unique cleavage by particular enzymes, detailed restriction maps, a comparison of enzymatic activities, or antibody cross-reactivity (see page 1110 of the FR Notice). If binding specificity is one acceptable characteristic to be combined with sequence data and restriction maps for satisfaction of the written description requirement, then hybridization experiments showing specific hybridization of an isolated nucleic acid with related nucleic acids in other animal species should also be sufficient.

The appellant believes that the Synopsis of Application of Written Description Guidelines available on the U.S. Patent & Trademark Office's internet site (attached as Exhibit H) supports the appellant's position. Indeed, according to this Synopsis published by the Office, it is perfectly acceptable to define claimed genetic sequences in terms of the hybridization conditions disclosed in the specification. For instance, in Example 9 of the Training Examples provided in the Synopsis beginning on page 35,[1] an example is provided where the specification discloses a single cDNA (SEQ ID NO: 1) encoding a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity. The specification discloses that the complement of

[1] The Table of Contents of the Synopsis erroneously indicates that Example 9 begins on page 28.

SEQ ID NO: 1 was used under highly stringent hybridization conditions for the isolation of nucleic acids that encode proteins that bind to dopamine receptor. The hybridizing nucleic acids were not sequenced. The exemplary claim is directed to an isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO: 1, wherein the nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity.

Example 9 of the Synopsis acknowledges that the claim is drawn to a genus of nucleic acids all of which must hybridize with SEQ ID NO: 1 and must encode a protein with the same activity. The example also acknowledges that, in this instance, there is only a single species disclosed that is within the scope of the genus. Nevertheless, the example also notes that the art indicates that hybridization techniques using a known DNA probe under highly stringent conditions were conventional in the art at the time of filing (see Analysis beginning on page 36). The example further notes that a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claim because the highly stringent conditions set forth in the claim yield structurally similar DNAs. Thus, "a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of the DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention" (see sentence bridging pages 36-37).

Like the claim at issue in Example 9 of the PTO's Written Description Guidelines Synopsis discussed above, the inventions of appealed claims 4 and 24 are defined in terms of hybridization conditions that are specifically disclosed in the specification. The only difference is that the appealed claims are directed to isolated proteins encoded by the hybridizing nucleic acid sequences, and to methods of purifying the same. If a nucleic acid that hybridizes under specifically disclosed stringent conditions to a nucleic acid that is specifically disclosed in the specification is adequately described by the specification (as exemplified in the Synopsis Example 9), and the specification teaches methods for purifying the encoded proteins by recombinantly expressing the described nucleic acid sequences, then it follows that the proteins are also adequately described. Indeed, hybridization techniques using a known DNA probe

under highly stringent conditions were conventional in the art at the time of filing, and a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claim because the highly stringent conditions set forth in the claim yield structurally similar DNAs. Therefore, based on the teachings of the Synopsis of Application of Written Description Guidelines, appealed claims 4 and 24 (and the claims dependent thereon) should be found to have written description support in the specification.

Thus, the present specification describes the hybridization conditions that may be used to detect cross-species hybridization of a GDF-1 probe. The present specification also makes it clear that the contemplated invention is the genus of mammalian GDF-1 proteins. The skilled artisan, having full knowledge of the teachings of Sambrook *et al.* described above, would immediately see that the disclosed GDF-1 nucleic acid could be used to detect GDF-1 cDNA sequences from other species using the same hybridization techniques, and that such cDNAs could be sequenced to determine the encoded amino acid sequence. Again, according to the Written Description Guidelines (page 1099), the skilled artisan incorporates the knowledge of such common techniques into his understanding as to what the inventor possessed at the time of filing.

The Examiner responded to appellant's arguments by noting that appellant is arguing enablement rather than written description (Office Action, March 12, 2002, page 7). Appellant respectfully notes, however, that appellant's arguments are based on the written description guidelines promulgated by the Office, and are therefore pertinent to written description of the invention. In view of the remarks above, the appellant submits that the specification provides defining structural features of a GDF-1 gene so as to provide support for the claimed genus, and furthermore, that the skilled artisan would immediately recognize that the appellant was in possession of the claimed genus at the time the application was filed.

(3) New Matter

The Examiner indicated in the Office Action dated October 21, 2002, that the rejection under 35 U.S.C. §112, first paragraph, is both a written description rejection and a new matter rejection (see page 3), presumably because appellant has allegedly failed to point to a page and

line number for support for claims 34-35, as originally requested in the Office Action dated March 12, 2002 (bottom of page 6). At the outset, it should be noted that the limitations of claims 34 and 35 have been incorporated into claims 4 and 24 by way of the after final amendment submitted concurrently with this appeal brief. Therefore, this new matter rejection is now pertinent to claims 4 and 24.

In maintaining this aspect of the written description rejection, the Examiner appears to have ignored the appellant's remarks in the Reply filed July 12, 2002, providing the page and line number in support of claims 34-35 (now amended claims 4 and 24) (see paragraph bridging pages 7-8). Appellant again notes that the requisite support may be found on page 10, lines 8-9, where it is disclosed that 20X SSC is defined as 3M sodium chloride/0.3M sodium citrate. So, by extension, 2X SSC would be defined as stated in claim 39. Page 9, lines 11-12 give support for washing at 68°C in 2X SSC, and page 17, lines 9-13 provide support for hybridization at 65°C.

In view of the above remarks, the appellant respectfully submits that amended claims 4 and 24 contain no new matter, and furthermore that the claims fully satisfy the requirements of §112, first paragraph.

Summary

In summary, the appellant submits that his invention is supported by a specific, substantial and credible utility such that the skilled artisan would know how to use the claimed invention. The appellant further submits that the specification provides defining structural features of a GDF-1 gene so as to provide support for the claimed genus, and furthermore, that the skilled artisan would immediately recognize that the appellant was in possession of the claimed genus at the time the application was filed.

Accordingly, it is submitted that the Examiner's §§101 and 112 rejections of the claims are in error and should be reversed.

Respectfully submitted,

MORGAN LEWIS & BOCKIUS LLP

By _____
Bonnie Weiss McLeod
Reg. No. 43,255

1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Phone: (202) 739-3000
Facsimile: (202) 739-3001
Direct: (202) 739-6150